

REMARKS

The following is in response to the Office Action mailed July 20, 2004

Applicants are hereby affirming the provisional election made on May 13, 2004 to prosecute Group III, claims 77-93 and linking claims 1 and 94-97 to the degree applicable. Applicants reserve the right to file divisional applications on all non-elected subject matter of the instant application.

Claims 1, 77-93, and 94-97 are under examination. Claim 78 has been cancelled, Claims 1, 77, 79, 81, 82, 83, 85, 87, 89, 91, 92, 93, 94, 95, 96 and 97 have been amended. New claims 98 and 99 have been added.

Defective Oath

The Oath or Declaration was objected as defective because it did not include signatures of all the inventors. During a telephone conversation with the Examiner, on October 12, 2004, it was clarified that (i) two declarations were submitted on January 26, 2004 (8 pages) which included all the inventor's signatures, and (ii) the submission of a new Oath or Declaration was not required.

Objections

The Abstract of the Disclosure was objected (Office Action page 2) because it did not meet the requirements of MPEP 608.01b. The Abstract has been replaced providing text that defines the variables.

Disclosure was objected (Office Action page 5) because definitions of variables X1 to X4 (of claim 1) were technically erroneous and incomplete without the proviso suggested by the Examiner. Applicants agree with the Examiner and have included the proviso in "Summary of the Present Invention" and in "Detailed Description of the Present Invention", which are parts of the specification where there is a broad description of the compounds. However, Applicants respectfully submit that the proviso is not needed in Claim 1 in view of the amendments therein.

Claim 1 was objected for informalities (Office Action page 8). Claim 1 has been amended to read -- or is a single bond -- as suggested by the Examiner.

Applicants respectfully submit that all Objections have been properly addressed and request their withdrawal.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1 and 77-93 are rejected as containing subject matter not properly described in the specification (Office Action page 5)

The Office Action states that definitions of substituents in claim 1 and claims 77-93 are directed to a vast number of chemical compounds, which have not been described in the instant application in a manner permitting the ordinary practitioner to have the guidance necessary to make a very large proportion of the compounds encompassed.

Applicants have amended Claim 1 to conform with the elected subject matter and to limit the number of substituents. As amended, Claim 1 discloses more specifically the compounds exemplified in the disclosure.

Claims 95-97 are rejected under 35 U.S.C. § 112, first paragraph (Office Action page 6) as containing subject matter that was not described in the specification in a way to enable one of ordinary skill in the art to make and/or use the invention. Examiner listed the *In re Wands* factors to determine if a conclusion of “undue experimentation” was appropriate. Examiner contends (page 6, point A) that the breadth of claim 95 is directed to an intermediate set of disease conditions defined only by the VR1 receptor. Claim 95 has been amended to a limited number of disorders that can be ameliorated or treated by inhibiting or antagonizing activity directed to the VR1 receptor (see paragraph 1 to paragraph 4 on page 35 of the present Application). Applicants believe that the amendment to Claim 95 informs the skilled in the art on the full scope of the present invention without the need of “undue experimentation”. Claims 96 and 97 are directed to specific disorders on the urinary tract. New claims 98 and 99 are directed to ameliorating pain and inflammatory thermal hyperalgesia, respectively. Applicants sustain that the two new claims do not represent new matter. Methods to treat pain and to treat inflammatory thermal hyperalgesia with the compounds of the present disclosure were described in the specification (page 21 fourth paragraph, and seventh and last paragraph, respectively; see also page 34 last paragraph and page 35 paragraph 1 to paragraph 4).

Examiner considers the state of prior art based on Reference N. Applicants respectfully state that reference N is not prior art to the present application. Examiner is respectfully directed to the discussion on the first paragraph under “Rejections under 35 U.S.C. § 102.”

The Office Action states (page 7 point F) that the amount of direction provided by the disclosure with regard to both *in vivo* and *in vitro* pharmaceutical activity is only generic, i.e. no specific pharmaceutical activity has been provided for any one of the compounds the preparation has been disclosed in the specification. Applicants respectfully disagree with this observation. The specification of the present application discloses a range of IC₅₀ values (for the *in vitro* activity assay) for the compounds of the present invention (second paragraph of page 34). Nine (9) of the sixty-seven (67) indazolylurea compounds tested according to the protocol described in the specification (page 32-33) had IC₅₀ values of 397 – 15 nM. Applicants respectfully maintain that disclosure of pharmacological activity or structure-activity relationship is not required by law for each specific compound to satisfy the enablement requirement.

The Office Actions states (page 7 point H) that the quantity of experimentation needed to make or use the invention based on the content of the disclosure is deemed to be excessive in the area of medicinal administration of the claimed substituted indazoles because of the complete lack of guidance in the form of test data. Applicants would like to reference *Cross v. Iizuka*, 224 U.S.P.Q 739-749 (1985). In that case Appellee Iizuka sought to rely on a Japanese patent application priority date. As described by the court, “the Japanese priority application . . . discloses utility for the . . . compounds [at issue] . . . both as an inhibiting agent for thromboxan[e] synthetase in human or bovine platelet microsomes . . . and as therapeutically active agents . . . functioning as a medicine preventing deleterious conditions caused by thromboxane A2 . . .” *Id.* at 743. However, the only evidence presented to support efficacy was in the form of *in vitro* data showing a 25 nM IC₅₀ inhibitory effect for a particular imidazole derivative that was outside the scope of the count. At issue was whether this showing was sufficient to support the utility requirement under § 101 and the enablement requirement under § 112, first paragraph. The Court reasoned that the disclosed concentration would provide sufficient

information as to an initial dosage level so that one skilled in the art could determine, without undue experimentation, the necessary concentration of the rest of the imidazole compounds, and would provide sufficient guidance to enable one of skill in the art, without undue experimentation, to use the compounds in that particular assay. *Id.* at 748. Accordingly, Applicants maintain that the law does not require the disclosure of the activity of each and every compound of the specification to have enablement to support claims directed to methods of medicinal treatment, and respectfully submit that the data disclosed in the present specification provides sufficient direction with regards to the pharmacological activity of the claimed compounds.

Claims 95 is rejected under 35 U.S.C. § 112, first paragraph (Office Action page 7), as containing subject matter that was not described in the specification as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully disagree with the Examiner's contention. Claim 95 has been amended to a limited number of disorders, which can be ameliorated or treated by inhibiting or antagonizing activity directed to the VR1 receptor. The present application discloses evidence of the results of the *in vitro* assays, which clearly indicate that the tested indazole compounds of the present invention have a biological activity as antagonists of the VR1 receptor (see page 34, second paragraph). Furthermore, the present disclosure cites a series of references (see page 35 of the present application), which indicate the involvement of the VR1 receptor in several of the disease states disclosed in the present application. Applicants, would like to cite some of these references (also included in the Information Disclosure Statement): Nolano *et al.* (C9) describes involvement of capsaicin in the painful sensations evoked by noxious thermal and mechanical stimuli; David *et al.*, (C6) describes the essential role of the VR1 receptor un inflammatory thermal hyperalgesia; Caterina *et al.*, (C3) describes the involvement of the VR1 receptor as a transducer of painful thermal stimuli *in vivo*; Fowler (C7) describes the effects of excess capsaicin on urinary bladder, causing desensitization and therefore improving the urinary bladder capacity. With this information, a skilled in the art would understand that the inventors, at the time the application was filed, were in possession of antagonists to the VR1 receptor that had

analgesic activity and that would be useful to treat or ameliorate the disorders claimed in the present application. Accordingly, Applicants respectfully request that in view of the foregoing amendments and remarks the Examiner withdraw the rejections under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 77, 79, 80, 81, 85, 89, 92, and 94-97 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention (Office Action page 8).

Claim 1 has been amended to limit variable “m” to integers of 1-6 as suggested by the Examiner.

The Office Action requires clarification as to the intended meaning of the terms “1-azepanyl” and “1-azocanyl”. Definitions for the terms “1-azepanyl” and “1-azocanyl” have been added to the appropriate section of the “Detailed Description of the Present Invention” (under “definition of Terms”).

Claims 79, 81, 85, 89, and 92 are rejected (Office Action page 8, last paragraph) as technically incorrect regarding the language “1, 2, or 3 substituents...consisting of hydrogen...” wherein the group being substituted is phenyl. Applicants respectfully submit that among the choices of substituents for the R9 group (aryl or heterocycle) in claims 79, 81, 85, 89, and 92, hydrogen is not present. Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

Claims 94-97 are rejected (Office Action page 9, first paragraph) as incomplete because the term “compound of formula (I) is not defined in said claims or by dependence from another claim. Applicants have amended claims 94-97 to provide proper dependence from claim 1. The language “as defined in claim 1” has been added to claims 94-97.

In view of the foregoing amendments and remarks, Applicants respectfully request that the Examiner withdraw all rejections under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 102.

Claims 1 and 77-97 are rejected under 35 U.S.C. § 102(a) as being anticipated by Sumimoto Pharm. Co. EP 1 403 255 (PTO-892 Ref. N). Applicants respectfully disagree.

The legal standard for anticipation is that a claim is anticipated only when a single prior art reference discloses each and every limitation in the claim. Applicants respectfully submit that reference N does not fulfill this legal requirement. Claims 1 and 77-97 of the present application claim compounds of formula (I) and their use to treat or prevent a series of disorders that can be ameliorated by inhibition of the vanilloid receptor subtype 1 (VR1). Reference N does not anticipate the present claims for the following reasons: (i) Claim 1 of the present application has been amended to limit the definitions of X₅, Z₁ and Z₂ to form a urea group. Reference N does not teach indazolylylureas as the present application does. Reference N does not define substituent R1-X (in claim 2, 24 and 28) as forming a urea group like the compounds of the present application.; (ii) Reference N teaches compounds of formulas 1-5 that are inhibitors of Rho kinase. The compounds of the present invention claim compounds that are antagonists of the VR1 receptor; (iii) Reference N teaches the use of pharmaceutical compositions to treat urinary incontinence using compounds that have inhibitory activity against Rho kinase. Reference N does not teach the use of indazolylylureas as antagonists of the VR1 receptor to treat pain, urinary disorders and hyperalgesia as the present application does. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Claims 1, 77, and 94 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kirchner (US Patent No. 3,647,819, PTO-892 ref. C). The legal standard for anticipation is that a claim is anticipated only when a single prior art reference discloses each and every limitation in the claim. Applicants respectfully submit that reference C does not fulfill this legal requirement. (i) Claims 1 and 77 of the present application claim compounds of formula (I) in which the -NH(O)NH- group attached to the phenyl group of the indazol nucleus is linked to a R9 group - that can be aryl or heterocycle - through an alkenylene, alkylene, piperazine or other group. The compounds of formula A, B, or C of reference C do not have a linking group between the aryl group and the -NH(O)NH-

attached to the indazol molecule; (ii) Substituent R_B of reference C is a substituted or unsubstituted phenyl. R₃ in claims 1 and 77 of the present invention (which corresponds to substituent R_B of reference C), is never a phenyl group. Therefore, Applicants respectfully submit that reference C does not anticipate the present claims 1 and 77 and request the withdrawal of the rejection.

Claims 1 and 77 are rejected under 35 U.S.C. § 102(b) as being anticipated by Biller *et al.*, US Patent No. 5,760,246 (PTO-892 ref. J). The legal standard for anticipation is that a claim is anticipated only when a single prior art reference discloses each and every limitation in the claim. Applicants respectfully submit that reference C does not fulfill this legal requirement. Reference J discloses compounds with focal nucleus -L2-A-C(O)-B-L1-, in which A can be a substituted N, but B is always a mono-, bi- or tricyclic group. The compounds of Reference J cited by the Examiner have indazol groups, however, the compounds fail to teach a three-member urea group as in the compounds claimed in claims 1 and 77.

Accordingly, Applicants respectfully submit that reference J does not anticipate the present claims 1 and 77 and request the withdrawal of the rejection.

Claims 1, 77 and 94-97 are rejected under 35 U.S.C. § 102(e) as being anticipated by SmithKline Beecham International application WO 03/022809 (PTO-892 Ref. L). Applicants respectfully disagree because reference L does not qualify as prior art. Reference L is a WIPO publication of an international application filed on September 13, 2002. A WIPO publication that was filed after November 29, 2000, that designates the U.S. and that is published in English has a 35 U.S.C. § 102(e) prior art date of the international filing date or earlier effective U.S. filing date. In this case the international filing date of reference L is September 13, 2002, which is after the date of the priority claimed by the present application. Foreign priority dates are not to be considered in rejections under 102(e) for WIPO publications filed after November 29, 2000 (MPEP 706.02(f)(1)). The present application claims priority on U.S. Application No. 60/358,220 filed on February 20, 2002. Claims 1, 77 and 94-97 are fully supported in the specification and claims of U.S. Application No. 60/358,220. Accordingly, Applicants

respectfully submit that reference **L** does not qualify as prior art and the withdrawal of the rejection is respectfully requested.

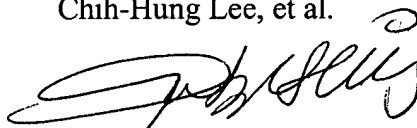
Claims 1 and 77 are rejected under 35 U.S.C. § 102(b) as being anticipated by Lichtenthaler and Moser (PTO-892 ref. **R**). The legal standard for anticipation is that a claim is anticipated only when a single prior art reference discloses each and every limitation in the claim. Applicants respectfully submit that reference **R** does not fulfill this legal requirement. Compounds "27" and "28" disclosed on page 4398 of reference **R** do not have the urea group that characterizes the indazolylureas claimed in claims 1 and 77 of the present invention. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Conclusions

In view of the amendments and the aforementioned remarks, Applicants respectfully believe that the application is in condition for allowance and respectfully request that the Examiner withdraw all outstanding rejections and passes this application to allowance.

Should the Examiner have any concerns regarding the above, he is respectfully requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,
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